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Review

Mitochondria and viruses

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ABSTRACT

Mitochondria are involved in a variety of cellular metabolic processes, and their functions are regulated by extrinsic and intrinsic stimuli including viruses. Recent studies have shown that mitochondria play a central role in the primary host defense mechanisms against viral infections, and a number of novel viral and mitochondrial proteins are involved in these processes. Some viral proteins localize in mitochondria and interact with mitochondrial proteins to regulate cellular responses. This review summarizes recent findings on the functions and roles of these molecules as well as mitochondrial responses to viral infections.

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Contents

1. Introduction

Mitochondria are involved in a variety of cellular metabolic processes including ATP production, calcium homeostasis, cell proliferation, programmed cell death, and the synthesis of amino acids, nucleotides, and lipids. Although each mitochondrion has its own genome, most mitochondrial proteins are encoded by nuclear

Abbreviations: ANT, adenine nucleotide translocator; CARD, caspase recruitment domain; HSV, herpes simplex virus; IFN, interferon; MAVS, mitochondrial antiviral signaling protein; MFN, mitofusin; MMP, mitochondrial membrane permeabilization; PTPC, permeability transition pore complex; RIG-I, retinoic acid-inducible gene-I; STING, stimulator of IFN genes; TLR, toll-like receptor; VDAC, voltage-dependent anion channel; vMIA, viral mitochondria-localized inhibitor of apoptosis; VSV, vesicular stomatitis virus.

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DNA. The distribution, shape, and functions of these organelles are regulated by extrinsic and intrinsic stimuli, which in some cases include viruses.

Viruses are very small, noncellular parasites that only replicate in living cells using energy sources and molecular components produced by the host cell. Viral infections induce a variety of outcomes in eukaryotic cells depending on the cell type, the virus, and the conditions at the time of infection. Although eukaryotic cells have a number of antiviral defense mechanisms, viruses have developed various countermeasures to evade host responses. Among the primary host defense mechanisms, programmed cell death (apoptosis) and the interferon (IFN) system are particularly important to combat viral infections. Interestingly, recent studies have revealed that mitochondria play a central role in host antiviral responses, and a number of viral proteins localize in mitochondria and interact with mitochondrial proteins. In this article, we review recent findings on mitochondrial responses to viral infections.

2. Innate immune responses to viral infections

Once viruses infect their hosts, the host defense system promptly recognizes pathogen-associated molecular patterns (PAMPs), which include genomic nucleic acids, structural proteins, and transcriptional products. Pattern recognition receptors (PRRs) detect PAMPs of viral components and then activate signaling pathways leading to the production of IFNs, inflammatory cytokines, and chemokines (Takeuchi and Akira, 2009). There are three types of PRRs: toll-like receptors (TLRs), retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs), and nucleotide oligomerization domain (NOD)-like receptors (NLRs). TLRs are presented predominantly in immune cells and are comprised of leucine-rich repeats (LRRs), a transmembrane domain, and a cytoplasmic domain. Five types of TLRs recognize the structural motifs of viral components. TLR2 and TLR4, which are presented on the cell surface, recognize viral envelope proteins. TLR3, TLR7, and TLR9, which are localized on cytoplasmic vesicles such as endosomes and the endoplasmic reticulum (ER), recognize viral nucleotides including double-stranded RNA, single-stranded RNA, and nonmethylated CpG DNA (Takeuchi and Akira, 2009). RLRs include RIG-I, melanoma differentiation-associated 5 (MDA5), and laboratory of genetics and physiology-2 (LGP2) (Kang et al., 2002; Kovacsovics et al., 2002; Yoneyama et al., 2005, 2004). Excluding LGP2, RLRs are composed of a DExD/H box RNA helicase domain, a C-terminal repressor domain, and two N-terminal caspase recruitment domains (CARDs). LGP2 lacks CARDs and is composed of an RNA helicase domain and a C-terminal repressor domain. RIG-I and/or MDA5 function as cytoplasmic RNA sensors to induce the production of type I IFN in nonimmune cells (Takeuchi and Akira, 2009). NLRs are a large family of cytosolic nucleotide sensors and are composed of a C-terminal LRR, a central NOD domain, and a variable N-terminal protein–protein interaction domain. Expressed in many cell types, NLRs regulate the production of proinflammatory cytokines by activating caspase-1, which cleaves and activates the secreted cytokines interleukin-1β and interleukin-18 (Bryant and Fitzgerald, 2009).

The signals initiated by TLRs and RLRs result in the transcriptional activation of genes encoding type I IFNs, inflammatory cytokines, and chemokines. In particular, mitochondria have been shown to be a key location for RLR-signaling pathways, thus we focused here on signaling that induces type I IFNs via cytoplasmic RLRs.

2.1. Mitochondria serve as an IFN-signaling platform

RLRs are cytoplasmic proteins, and RIG-I and/or MDA5 detect cytoplasmic viral RNAs. RIG-I is essential for the production of IFNs in response to such RNA viruses as paramyxoviruses, influenza virus, and Japanese encephalitis virus, whereas MDA5 is critical for immune responses to picornavirus (Kato et al., 2006). RIG-I recognizes the uncapped, unmodified 5′-triphosphate end of RNA generated by viral polymerases, but this molecular signature is absent in picornaviruses (Hornung et al., 2006).

DNA viruses (*e.g.*, adenovirus, herpes simplex virus type 1 [HSV-1], and Epstein–Barr virus [EBV]) induce IFN-β expression in a RIG-I-dependent manner (Cheng et al., 2007; Rasmussen et al., 2007; Samanta et al., 2006). EBV produces small RNA molecules that induce RIG-I-mediated IFN production (Samanta et al., 2006). Recently, Chen and colleagues reported that DNA-dependent RNA polymerase III (Pol-III), which is responsible for synthesizing 5′-triphosphate RNA from cytosolic poly(dA-dT) DNA, is a potent mediator of RIG-I signaling induced by HSV-1 or adenovirus infection (Chiu et al., 2009). These studies indicate that RLRs are important cytoplasmic detectors of DNA and RNA viruses.

Some molecules have been identified as signal transducers downstream of RIG-I and MDA5. IFN-β promoter stimulator 1 (IPS-1; also referred to as mitochondrial antiviral signaling protein [MAVS], Cardif, or VISA) was characterized as a RIG-I binding protein (Kawai et al., 2005; Meylan et al., 2005; Seth et al., 2005; Xu et al., 2005). IPS-1/MAVS consists of a C-terminal effector domain and an N-terminal CARD that interacts with two CARDs from RIG-I or MDA5. Interestingly, it has been demonstrated that IPS-1/MAVS is localized on the outer membrane of mitochondria (Seth et al., 2005). After activation by RLRs, IPS-1/MAVS recruits downstream signaling molecules from various cascades to activate and translocate transcription factors (*e.g.*, IRF-3 or NF-κB), resulting in the production of type I IFNs (Fig. 1). Moreover, recent reports suggest that two other mitochondria-associated proteins—stimulator of IFN genes (STING), which resides mainly in the ER, and the mitochondrial tethering protein mitofusin 2 (MFN2)—are involved in RLR signaling as signal transducers or MAVS-interacting proteins (Ishikawa and Barber, 2008; Yasukawa et al., 2009; Zhong et al., 2008). These findings show that mitochondria are key organelles for innate immunity that activate the production of IFNs.

Autonomous inhibition of RLR-induced signals is necessary to prevent pathologically excessive responses and the development of autoimmune disease, and the negative regulators of RLR-induced signals have recently been identified. LGP2, which does not contain a CARD, coimmunoprecipitates with MAVS and competes with the downstream kinase IKKε for a common interaction site on MAVS (Komuro and Horvath, 2006). The C-terminal region of LGP2 associates with and inhibits auto-oligomerization of RIG-I (Saito et al., 2007). NLRX1, a member of the NLR family, is localized on the mitochondrial outer membrane where it interacts with MAVS. Functional analyses suggested that NLRX1 acts as a negative regulator of RLR-MAVS-mediated antiviral signaling (Moore et al., 2008). The Atg5–Atg12 conjugate, a key regulator of autophagy, has also been shown to inhibit RLR signaling by directly binding to RIG-I, MDA5, and IPS-1 (Jounai et al., 2007). Autophagy is a physiologically and immunologically controlled intracellular homeostatic pathway that sequesters and degrades macromolecular aggregates, cellular organelles such as mitochondria, and whole microbes or their products (Delgado et al., 2009). Iwasaki and colleagues observed increased levels of mitochondrial mass and the accumulation of damaged mitochondria in Atg5-deficient cells, suggesting that absence of autophagy resulted in reactive oxygen species-dependent amplification of RLR signaling (Tal et al., 2009). Fig. 1 depicts mitochondrial proteins involved in the induction and inhibition of innate immune responses to viral infections.

2.2. Mitochondria-associated adaptor proteins

2.2.1. MAVS and IFN-β production

MAVS consists of 540 amino acid (aa) residues and contains three functional domains. These include an N-terminal CARD (aa 10–77) and a C-terminal transmembrane domain (aa 514–535). These two domains are connected via a proline-rich region (aa 103–173) that

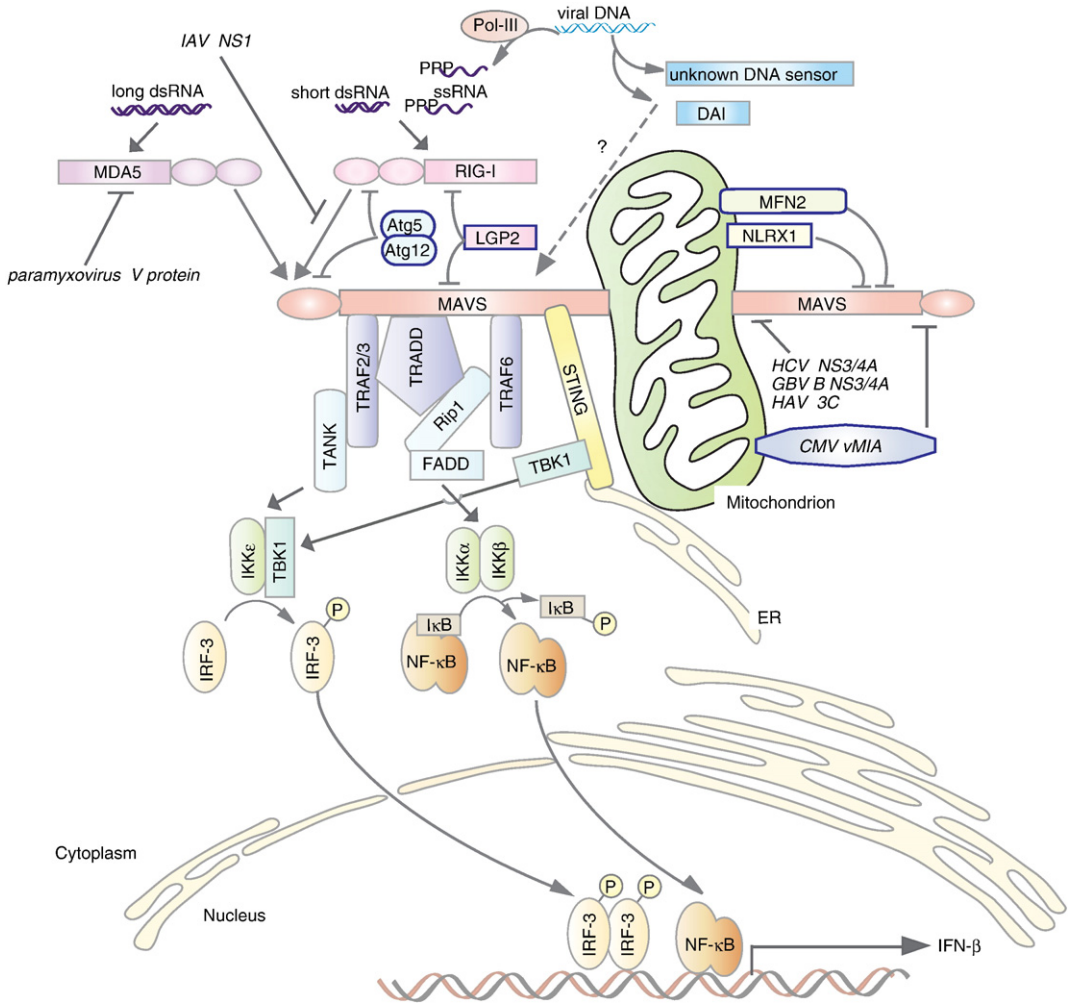

Fig. 1. RLR-mediated viral recognition and pathways leading to IFN-β production. Cytosolic viral RNA and DNA are recognized by RIG-I, MDA5, DAI, or other unknown DNA sensors. Cytosolic double-strand DNA is recognized by cytosolic DNA receptors such as DAI, or, in another pathway, cytosolic DNA-dependent RNA polymerase III (Pol-III) synthesizes 5′-triphosphate single-stranded RNA, which is recognized by RIG-I. RIG-I and MDA5 recognize long or short viral double-stranded RNA (dsRNA) or 5′-triphosphate single-stranded RNA (ssRNA) via their C-terminal RNA helicase domain. The two N-terminal caspase recruitment domains (CARDs) then interact with an N-terminal CARD from mitochondrial antiviral signaling protein (MAVS; also referred to as IPS-1, Cardif, and VISA). Anchored to mitochondria via a C-terminal transmembrane domain, MAVS receives signals from RLRs via a CARD and transduces the signal to downstream proteins via other regions including a proline-rich region that interacts with tumor necrosis factor receptor-associated factor 2 (TRAF2) and TRAF3 and a central region that interacts with tumor necrosis factor receptor associated-death domain (TRADD) and TRAF6. TRAF2 and TRAF3 interact with TRAF family member-associated NF-κB activator (TANK). TANK recruits a kinase complex composed of TANK-binding kinase 1 (TBK1) and IKKε, which phosphorylates IRF3 and activation of IFN-β transcription. TRADD interacts with TRAF3 and Rip1, whereas TRAF6 interacts with Rip1. Rip1 mediates signals between Fas-associated protein with death domain (FADD) and IKKα and IKKβ, leading to activation of the transcription factor NF-κB. Negative regulators of MAVS-mediated signals are also shown. Interactions between laboratory of genetics and physiology 2 (LGP2) and MAVS or RIG-I antagonize RIG-I/MAVS-mediated signaling. NLRX1 localizes to mitochondria and interacts with MAVS, leading to inhibition of signaling. Mitofusin 2 (MFN2), a mitochondrial tethering GTPase, interacts with MAVS via the heptad region of MFN2, which interferes with interactions between MAVS and various downstream molecules. The autophagic regulator protein conjugate Atg5/Atg12 also inhibits MAVS signaling. Several viral proteins inhibit MAVS-mediated signals. Nonstructural protein 1 (NS1) from influenza A virus, for instance, may interfere with the interaction between RIG-I and MAVS. MAVS is cleaved by viral proteases, including NS3/4A from hepatitis C virus and GB virus B, and 3C protein from hepatitis A virus. Cleaved MAVS does not transmit signals downstream or localize to mitochondrial membranes.

functions as the third domain (Kawai et al., 2005; Seth et al., 2005). The CARD of MAVS interacts with those of RLRs, such as RIG-I and MDA5. MAVS is anchored to the mitochondrial outer membrane via its C-terminal transmembrane domain, which is structurally similar to transmembrane domains of other mitochondrial proteins such as Bcl-xL, Bcl-2, and TOM20 (Seth et al., 2005). A C-terminal-truncated form of MAVS, which lacked the transmembrane domain, was detected in the cytosol and failed to mediate RIG-I/MDA5 signaling. Recent studies demonstrated that homodimerization of MAVS via its transmembrane domains is critical for innate immune signaling (Baril et al., 2009; Tang and Wang, 2009). The proline-rich region in MAVS mediates binding to the tumor necrosis factor (TNF) receptor-associated factor (TRAF) family proteins TRAF2, TRAF3, and TRAF6 (Saha et al., 2006; Xu et al., 2005). MAVS lacking the proline-rich region, however, is still capable of activating IFN-β production (Seth et al., 2005). TNF receptor-associated death domain (TRADD) also interacts with MAVS via the central region. Tschopp and colleagues demonstrated that the level of IFN-β production induced by vesicular stomatitis virus (VSV) infection was lower in TRADD-deficient mice and suggested that TRADD recruits TRAF3/TRAF family member-associated NF-κB activator (TANK) and FADD/RIP1 to form a larger complex, leading to activation of IRF3 and NF-κB (Michallet et al., 2008).

Another function of MAVS was identified by the investigation of truncated MAVS derived from splicing variants. Li and colleagues reported that MAVS splicing variants 1a (exon 2 deletion) and 1b (exon 3 deletion), due to a frame shift by exon deletion, consist of 131 aa and 124 aa residues, respectively (Lad et al., 2008). Both MAVS 1a and 1b contain the putative CARD, which enables them to receive RLR signals. However, MAVS 1a and 1b show opposite effects on RLR-MAVS-mediated IFN production. MAVS 1a lacks the signaling domain to transmit signals downstream and acts as a competitor in MAVS

full length-mediated signaling. MAVS 1b can interact with FADD and RIP1 (downstream of RLR signaling) and selectively activate IFN-β production (Lad et al., 2008). These results suggest that MAVS signaling can be negatively regulated by its own splice variants.

2.2.2. STING

STING (also called MITA, MPYS, and ERIS) was identified as an adaptor in the antiviral pathway leading to IFN-β expression (Ishikawa and Barber, 2008; Jin et al., 2008; Sun et al., 2009; Zhong et al., 2008). Zhong and colleagues showed that MITA/STING was anchored to the mitochondrial outer membrane and that it induced IFN-β production by interacting with MAVS (Zhong et al., 2008). Ishikawa and colleagues, however, reported that STING was located on the ER (Ishikawa and Barber, 2008) and translocated from ER to Sec-5-containing vesicles in response to HSV-1 infection, suggesting that STING functions in DNA-mediated innate immunity (Ishikawa et al., 2009). It has also been demonstrated that STING translocates from ER to the Golgi apparatus and colocalizes with TBK1 (Saitoh et al., 2009). Dimerization of ERIS/STING is critical for self-activation and IFN production (Sun et al., 2009). Thus, it is likely that STING serves as a molecular adaptor to mediate signaling at contact sites between mitochondria and ER.

2.2.3. MFN1 and MFN2

MAVS also interacts with MFN2, a mitochondrial outer membrane guanosine triphosphatase (GTPase). MFN1 and MFN2 have both been identified as dynamin-related GTPases. MFN1 plays a major role in mitochondrial fusion, whereas MFN2 tethers ER to mitochondria. MFN2 is enriched at the ER-mitochondria interface, and disruption of ER-mitochondria interactions are observed in mouse embryonic fibroblasts (MEFs) in which MFN2 expression has been silenced (de Brito and Scorrano, 2008). The Ras-binding domain of MFN2 is required for the tethering function (de Brito and Scorrano, 2009). Recently, Yasukawa and colleagues reported that MAVS-dependent activation of the IFN-β promoter was inhibited by coexpression of MFN2. Knockdown of endogenous MFN2 expression with siRNA enhanced IFN-β promoter activation induced by measles virus infection and poly(I:C). Heptad region 1 of MFN2 interacts with the central region of MAVS, which is necessary to interact with downstream effectors for IFN production, suggesting that MFN2 acts as an RLR signaling inhibitor (Yasukawa et al., 2009). In Sendai virus H4-infected cells, RLR activation promotes mitochondrial elongation mediated by MFN1, resulting in MAVS-STING interaction at the mitochondria-ER site (Castanier et al., 2010). Thus, MFN1 and MFN2 appear to play opposite roles in antiviral responses. These studies strongly suggest that the contact sites between ER and mitochondria and the mitochondrial-associated membrane play critical roles as signal mediators during host cell antiviral responses.

2.3. Viral evasion of host immune responses

Viruses have developed strategies to evade host immune responses including RLR-mediated IFN production. A number of viral gene products have been identified as inhibitors of RLR signaling. These proteins bind viral RNA, interfere with transcriptional factors downstream of RLRs, or regulate other mitochondria-associated signal transducers (Komuro et al., 2008) (Fig. 1). Because RLR signaling converges in mitochondria, it seems natural that viruses would target mitochondrial processes to evade this arm of immune responses.

Hepatitis C virus (HCV) encodes NS3/4A, a serine protease that specifically inhibits RIG-I-mediated signaling by cleaving MAVS at Cys508 (Li et al., 2005; Meylan et al., 2005). Cleaved MAVS can neither anchor to mitochondria nor mediate RIG-I signaling. A similar process has been described in *Flaviviridae* GB virus B (Chen et al., 2007) and *Picornaviridae* hepatitis A virus (HAV). HAV encodes serine protease 3C, which cleaves MAVS at Gln428, thereby blocking antiviral signaling (Yang et al., 2007). NS1, encoded by influenza A virus, interacts with RIG-I and inhibits RIG-I-mediated induction of IFN-β production. NS1 may interfere with signals from the RIG-I-STING complex via direct interactions (Mibayashi et al., 2007). V proteins encoded by paramyxoviruses interact with MDA5 and specifically inhibit MDA5-initiated IFN expression (Andrejeva et al., 2004).

Viral mitochondria-localized inhibitor of apoptosis (vMIA), which is encoded by UL37x1 from human cytomegalovirus (CMV), is a well-known antiapoptotic and mitochondria-associated protein (McCormick et al., 2003). Arnoult and colleagues recently demonstrated that overexpression of vMIA inhibits MAVS-induced activation of the IFN-β promoter and mitochondrial fragmentation (Castanier et al., 2010). Therefore, vMIA may regulate mitochondrial activities, resulting in inhibition of IFN production.

3. Apoptosis and viral infection

Apoptotic cell death is an early host cell response to viruses and IFN expression. Apoptosis can be triggered by two distinct, well-characterized signaling cascades: the extrinsic and intrinsic pathways (Galluzzi et al., 2008; Kroemer et al., 2007). The extrinsic pathway is triggered by binding of extracellular ligands to “death receptors,” including TNF receptor-1, CD95/Fas, and TNF-related apoptosis-inducing ligand (TRAIL) receptors-1 and -2. Ligand binding induces a caspase cascade, in which signals are transmitted via initiator caspase-8 and caspase-9 to effector caspase-3 and caspase-7, which cleave specific substrates. In the intrinsic pathway, mitochondria play pivotal roles in driving cell death. Following mitochondrial membrane permeabilization (MMP), the mitochondrial transmembrane potential ($\Delta\psi_m$) dissipates, intermembrane space proteins are released, and mitochondrial bioenergetic and redox-detoxifying activities are disrupted. The intermembrane space proteins include such caspase activators as cytochrome *c* (Liu et al., 1996), Smac/DIABLO (Du et al., 2000), and Omi/HtrA2 (Suzuki et al., 2001), as well as caspase-independent death effectors including apoptosis-inducing factor (AIF) (Susin et al., 1999) and endonuclease G (Li et al., 2001). These caspase activators activate caspase-9 and caspase-3. At later stages of apoptosis, oligomerized cytochrome *c*, caspase-9, and apoptosis protease activating factor 1 (APAF1) form a large structure called an apoptosome, which then activates effector caspases to produce the characteristic events of cell death (Cain et al., 2002). It should be noted that the two pathways are interconnected by caspase-8 and the proapoptotic protein Bid, which regulate MMP (Li et al., 1998). Apoptosis is induced by DNA damage, ER stress, lysosomal stress, reactive oxygen species, and calcium overload (Kroemer et al., 2007). In addition, during viral infection and replication, viruses co-opt host organelles and molecular machinery, which may be associated with events that induce MMP via the intrinsic pathway. Regulation of MMP allows viruses to control cellular viability effectively.

3.1. Mitochondrial homeostasis and viral infection

Three models have been proposed to explain the mechanism by which MMP induces apoptosis: (1) selective promotion of mitochondrial outer membrane permeabilization (Kuwana et al., 2002; Wei et al., 2001); (2) destabilization of the mitochondrial lipid bilayer (Basañez et al., 2002; Terrones et al., 2004); and (3) permeabilization of the mitochondrial inner membrane via activation of the permeability transition pore complex (PTPC) (Shimizu et al., 1999). Of note, proapoptotic or antiapoptotic proteins from the Bcl-2 family have been incorporated into all three models.

Bcl-2 was the first identified mammalian homolog of *ced-3*, an essential gene for cell death in *C. elegans* (Vaux et al., 1988). Bcl-2 contains four distinct Bcl-2 homology domains (BH1–4). The Bcl-2 family is composed of three subfamilies: the antiapoptotic Bcl-2 subfamily (*e.g.*, Bcl-2, Bcl-xL), the proapoptotic BH1-3 domain-

containing Bax subfamily (*e.g.*, Bax and Bak), and the proapoptotic BH3-only subfamily (*e.g.*, Bid, Bad, and Bim). Bax and Bak assemble on the mitochondrial and ER membranes, where they function as channels or pores and mediate MMP, resulting in the release of cytochrome *c* and calcium, respectively (Kuwana et al., 2002; Nutt et al., 2002; Wei et al., 2001). Bcl-2/Bcl-xL forms an inhibitory antiapoptotic complex with activated Bax/Bak. One proapoptotic mechanism involves BH3-only proteins binding activated Bax/Bak instead of the repressor Bcl-2/Bcl-xL (Chen et al., 2005). In the second model, Bax plays an important role in rapid transbilayer reorganization of lipids (Terrones et al., 2004), and the resulting curvature stress in the mitochondrial outer membrane induces the formation of large pores (Basañez et al., 2002). Permeabilization of the inner mitochondrial membrane via activation of PTPC is induced by specific stimuli such as calcium overload and reactive oxygen species (Deniaud et al., 2008). Furthermore, it has been suggested that PTPC is regulated by several factors including mitochondrial matrix proteins (*e.g.*, cyclophilin D), intermembrane space proteins (*e.g.*, creatinine kinase), and outer membrane-associated proteins (*e.g.*, peripheral benzodiazepine receptor [PBR]) (Galluzzi et al., 2008; Halestrap, 2009; Kumarswamy and Chandna, 2009). Moreover, Bax and Bcl-2/Bcl-xL have been shown to modulate PTPC activity. Numerous studies have identified viral antiapoptotic (Table 1) and proapoptotic proteins (Table 2), some of which exhibit Bcl-2 family-like functions or structures. We briefly summarize the functions of those viral proteins in the following section.

3.2. Viral antiapoptotic and proapoptotic proteins that target mitochondria

3.2.1. DNA viruses

Adenovirus (ADV) carries two characteristic oncogenes, E1A and E1B, which encode products that exhibit proapoptotic or antiapoptotic activity. E1A induces apoptosis by activating p53 or sensitizing cells to death receptor ligands (*e.g.*, TNF-α, FasL, and TRAIL) (White, 2001). Bik, a member of the BH3-only subfamily, plays a crucial role in ADV-induced apoptosis (Shimazu et al., 2007). Indeed, Bik is activated by ADV infection, and siRNA-mediated depletion of Bik inhibits apoptosis in ADV-infected cells (Subramanian et al., 2007). E1A-induced cell death is blocked by the E1B-19K protein, which was initially identified as a viral Bcl-2 homolog (White, 2001; White et al., 1991). Like Bcl-2, E1B-19K is primarily located near mitochondria, which allows E1B-19 K to inhibit multimeric pore formation by Bax subfamily members (Han et al., 1996).

Vaccinia virus—an orthopoxvirus—encodes three antiapoptotic proteins: CrmA, F1L, and N1. CrmA is a general caspase inhibitor (Ray et al., 1992), whereas the latter two are viral Bcl-2-type proteins. F1L is responsible for the remaining antiapoptotic activity in viruses lacking CrmA (Wasilenko et al., 2003). F1L localizes to the mitochondria via its C-terminal region and interferes with apoptosis by inhibiting the loss of the inner $\Delta\psi_m$ and the release of cytochrome *c* (Wasilenko et al., 2003). Recent studies have demonstrated that F1L contains highly divergent BH domains (Campbell et al., 2010; Kvansakul et al., 2008), which likely allow F1L to interact with Bak constitutively and prevent Bak activation. During infection, F1L replaces the functions of cellular antiapoptotic Bcl-2 family protein, Mcl-1 (Campbell et al., 2010). In addition, F1L binds and specifically inhibits caspase-9 (Zhai et al., 2010). These results suggest that F1L functions both as a suppressor of proapoptotic Bcl-2 family proteins and as an inhibitor of caspase-9, thereby neutralizing two sequential steps in the mitochondrial cell death pathway. Several F1L orthologs have been identified in other poxviruses such as variola virus, monkeypox virus, and ectromelia virus. The antiapoptotic activity of the ectromelia virus ortholog has been demonstrated (Wasilenko et al., 2003). The N1 protein encoded by the N1L gene is structurally similar to Bcl-xL and other members of the Bcl-2 subfamily. Moreover, N1 inhibits apoptosis by binding to BH-3 motifs of proapoptotic proteins (Cooray et al., 2007).

Myxoma virus (MXV) is a rabbit leporipoxvirus that induces a lethal syndrome characterized by disseminated tumor-like lesions

Table 1
Viral antiapoptotic proteins.

Virus	Protein	Cellular homolog	Partners	Intracellular localization
ADV	E1A	–	p53, BH-3 only subfamily	Cytoplasm
	E1B-19K	Bcl-2	Bax subfamily	Mitochondria
VACV	F1L	Bcl-2	Bax, caspase-9	Mitochondria
	N1	Bcl-2	BH-3 motif	Cytoplasm, mitochondria
	CrmA	–	Caspase	Cytoplasm, nucleus
MXV	M11L	Bcl-2	Bax, Bak, PBR	Mitochondria
ASFV	A179L	Bcl-2	Bid, Bax, Bak	Cytoplasm
	A224L	–	Caspase	Cytoplasm
CMV	vMIA (UL37x1)	–	Bax, ANT	Mitochondria
	vICA (UL36)	–	Bak, caspase-8	Cytoplasm
EBV	BHRF1	Bcl-2	Bim	Mitochondria
	EBNA3A, EBNA3C	–	Expression of Bim	Nucleus
	EBNA-LP	–	HAX-1	Cytoplasm
KSHV	KSBcl-2	Bcl-2	Bax, Bak	Cytoplasm
	K7	Bcl-2	Bcl-2, caspase-3, CAML	Mitochondria, ER, cytoplasm
	K13/vFLIP	–	Caspase-8	Cytoplasm
	K15	–	HAX-1	Mitochondria, ER
γHV-68	M11	Bcl-2	Bax, Bak	Cytoplasm, nucleus
	vMAP	–	Bcl-2, Bax, Bak	Mitochondria
HCV	E2	–	–	Cytoplasm
	NS2	–	CIDE-B	ER
	NS5A	–	–	ER

Abbreviations: ADV, adenovirus; VACV, vacciniavirus; MXV, mixoma virus; ASFV, African swine fever virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus; KSHV; γHV-68, gamma-herpesvirus-68; HCV, hepatitis C virus.

Table 2
Viral proapoptotic proteins.

Virus	Protein	Partners	Intracellular Localization
EBV	BALF1	Bax, Bak	Cytoplasm
HPV	E1^E4	Cytokeratins	Mitochondria, microtubule-associated
	E6	p53	Cytoplasm
	E7	–	Cytoplasm
HCV	NS3	Caspase-8	Cytoplasm
	NS4A	–	Mitochondria
VSV	M	Transcription of Bcl-2 family members	Cytoplasm, nucleus
	P	–	Cytoplasm
IAV	PB1-F2	VDAC1, ANT3	Mitochondria (inner membrane)
AEV	VP3	–	Mitochondria
	2C	Caspase-9, caspase-3	Mitochondria
SARS-CoV	7A	Bcl-xL	Golgi apparatus
	NSP15	–	Cytoplasm
HIV-1	Vpr	ANT, VDAC	Mitochondria, Cytoplasm, nucleus
	Tat	–	Cytoplasm, nucleus
	Nef	–	Cytoplasm
	Protease	–	Cytoplasm
HTLV-1	p13II	–	Mitochondria (inner membrane)
HBV	HBx	VDAC3, Hsp60	Mitochondria

Abbreviations: EBV, Epstein-Barr virus; HPV, human papiloma virus; HCV, hepatitis C virus; VSV, vesicular stomatitis virus; IAV, influenza A virus; AEV, avian encephalomyelitis virus; SARS-CoV, severe acute respiratory syndrome corona virus ; HIV-1, human immunodeficiency virus type 1; HTLV-1, human T lymphotropic virus type 1; HBV, hepatitis B virus.

and generalized immunosuppression. M11L, a protein in the mitochondrial outer membrane, has been shown to inhibit apoptosis by binding to the MMP-inducible, pore-forming proteins Bax and Bak (Opgenorth et al., 1992; Wang et al., 2004). Structural analysis has revealed that M11L is a Bcl-2 homolog that binds to Bax and Bak with affinities similar to those observed for cellular Bcl-2 and Bcl-xL (Douglas et al., 2007). M11L also prevents the release of cytochrome *c* and the dissipation of $\Delta\psi_m$. Moreover, M11L physically associates with PBR, which is localized on the mitochondria outer membrane and interacts with mitochondrial PTPC, voltage-dependent anion channel (VDAC), and adenine nucleotide translocator (ANT). Thus, M11L appears to regulate MMP by acting on PBR, a PTPC modulator (Everett et al., 2002).

African swine fever virus (ASFV) is a large double-stranded DNA virus that induces an acute disease in which apoptosis plays a central pathogenic role. A179L is an Bcl-2 homolog from ASFV that exhibits antiapoptotic activity (Brun et al., 1996). In addition, transient expression of A179L in Vero cells prevents apoptosis induced by active forms of Bid (truncated Bid) (Galindo et al., 2008). Interestingly, A179L targets upstream BH3 activators as well as Bax and Bak, the two core components of the proapoptotic machinery (Galindo et al., 2008). A224L is expressed in late stages and is a member of the inhibitor of apoptosis protein family. Its overexpression inhibits caspase activity and cell death induced by various stimuli (Nogal et al., 2001). A224L also activates the transcription factor NF-κB (Rodríguez et al., 2002), which may prevent apoptosis during late stages of infection.

Cytomegalovirus, a β-herpesvirus, has a number of sophisticated strategies to manipulate and evade host defense mechanisms. The highly conserved UL37 gene encodes vMIA, which is essential for viral replication. vMIA inhibits apoptosis induced by a number of stimuli including ligation of death receptor, infection with E1B-19K-deleted ADV, and exposure to cytotoxic drugs (Goldmacher, 2002). vMIA is localized on the mitochondrial membrane via a mitochondrial transmembrane domain and forms a complex with ANT, a constituent member of PTPC. It is thought that vMIA inhibits opening of PTPC and subsequent MMP by forming a complex with ANT (Goldmacher, 2002). vMIA also interacts with Bax, resulting in translocation of the complex to mitochondria and inhibition of pore formation with multimeric Bax (Arnoult et al., 2004). Because the antiapoptotic effects of vMIA are not observed in Bax-deficient cells, vMIA may exert its antiapoptotic functions solely by neutralizing Bax (Arnoult et al., 2004). Viral inhibitor of caspase-8 activation (vICA or UL36 protein) inhibits Fas/CD95-mediated apoptosis (Skaletskaya et al., 2001). Activation of caspase-8 causes crosstalk and activation of the intrinsic pathway via the generation and translocation of truncated Bid (tBid) (Galluzzi et al., 2008). UL36/vICA may inhibit MMP caused by the crosstalk effect. Murine CMV (mCMV) encodes an antiapoptotic protein called viral inhibitor of Bak oligomerization (vIBO). vIBO blocks Bak-mediated cytochrome *c* release and apoptosis, suggesting that vIBO and vMIA (m38.5 protein in mCMV) have complimentary effects (Cam et al., 2010). CMV infection protects cells from apoptosis induced by rotenone, a potent inhibitor of mitochondrial respiratory complex I. This protection is mediated by a virally encoded 2.7-kb RNA fragment (β2.7) that interacts with complex I and prevents localization of the essential subunit genes associated with retinoid/interferon-induced mortality-19 (GRIM-19). Thus, β2.7 RNA stabilizes mitochondrial respiratory chain complex I, resulting in consistent ATP production, cell survival, and completion of the viral life cycle (Reeves et al., 2007).

EBV is a γ-herpesvirus that establishes a latent infection in B lymphocytes and eventually transforms cells. This virus encodes two Bcl-2 homologs: BHRF1 and BALF1 (Altmann and Hammerschmidt, 2005; Bellows et al., 2002; Henderson et al., 1993). BHRF1 and Bcl-2 have similar localization profiles, three-dimensional structures, and positive effects on cell survival (Hickish et al., 1994; Huang et al., 2003). Indeed, BHRF1 suppresses MMP and apoptosis induced by such stimuli as c-myc activation (Fanidi et al., 1998), heterologous viral infection (Tarodi et al., 1994), gamma radiation, and antitumor chemotherapeutic drugs (McCarthy et al., 1996). BHRF1 markedly inhibits TRAIL-mediated apoptosis, followed by caspase-8 activation and loss of $\Delta\psi_m$ (Kawanishi et al., 2002). Unlike Bcl-2 and Bcl-xL, BHRF1 lacks an exposed, preformed BH-3 binding groove and thus cannot sequester and inhibit proapoptotic BH-3-only proteins (Huang et al., 2003). The ability of BHRF1 to bind proapoptotic BH-3-only subfamily member Bim, but not Bak, provides protection, however. Interestingly, a relatively small amount of Bim is bound by BHRF1 when compared to the level of Bim expression induced by apoptosis. Although the mechanism remains unclear, BHRF1 may function through Bim to block apoptosis (Desbien et al., 2009). BALF1, another Bcl-2 homolog, also interacts with proapoptotic Bax and Bak (Marshall et al., 1999) and may antagonize the effects of BHRF1 (Bellows et al., 2002), whereas the role of BALF1 during the viral life cycle is still controversial. In addition, the nuclear antigens EBNA3A and EBNA3C, both of which are required in lymphoblastoid cell lines, are antiapoptotic. EBNA3A and EBNA3C cooperate as major determinants in downregulating the expression of the BH-3-only subfamily member Bim (Anderton et al., 2008). Because Bim is a critical regulator of B-cell survival and is a tumor suppressor in B cells, depletion of Bim by the nuclear EBNA3 proteins may facilitate EBV-mediated lymphomagenesis. EBNA-leader protein (LP) interferes with host transcription and the cytoplasmic apoptotic machinery (Kawaguchi et al., 2000; Matsuda et al., 2003). EBNA-LP interacts with Bcl-2 via cellular HS1-associated protein X-1 (HAX-1), a mitochondrial inhibitor of apoptosis that is regulated by Omi/HtrA2 (Cilenti et al., 2004; Matsuda et al., 2003).

Kaposi's sarcoma-associated herpesvirus (KSHV), also called human herpesvirus 8 (HHV-8), is the causative agent in Kaposi's sarcoma. KSHV ORF16 encodes Kaposi's sarcoma-associated Bcl-2 (KSBcl-2), overexpression of which blocks apoptosis as efficiently as Bcl-2, Bcl-xL, or EBV BHRF1. The inhibitory mechanism of KSBcl-2 is different from that of Bcl-2 or Bcl-xL, as KSBcl-2 did not interact with other Bcl-2 family members (Cheng et al., 1997). KSHV K7 is structurally related to survivin-DeltaEx3, a splice variant of human survivin that protects cells from apoptosis via an undefined mechanism. K7 contains a mitochondria-targeting sequence, an N-terminal baculovirus inhibitor of apoptosis repeat (BIR) domain, and a putative BH2-like domain. The BIR domain of K7 mediates binding to the effector caspase-3. However, the K7 antiapoptotic activity also requires the BH2-like domain, which is essential for the interaction with Bcl-2 (Wang et al., 2002). Thus, K7 may act as an adaptor for Bcl-2. K7 can also modulate the intracellular calcium concentration by interacting with the cellular calcium-modulating cyclophilin ligand (CAML) (Feng et al., 2002) and protein linking integrin-associated protein and cytoskeleton 1 (PLIC1), a regulator of the ubiquitin system (Feng et al., 2004). These observations indicate that the mitochondrial membrane-associated protein K7 may provide a platform for antiapoptotic processes. KSHV encodes other antiapoptotic proteins including K13 (a viral Fas-associated death domain-like interleukin 1β converting enzyme inhibitory protein [vFLIP]) and the mitochondrial protein K15. The antiapoptotic activity of vFLIP/K13 has been attributed to inhibition of caspase-8 activation (Guasparri et al., 2004) and expression of antiapoptotic proteins via NF-κB activation (Sun et al., 2003). K15 localizes to mitochondria and ER and interacts with HAX-1 (Sharp et al., 2002), which can bridge Bcl-2 and EBNA-LP to promote cell survival (Matsuda et al., 2003).

Murine γ-herpesvirus 68 (γHV-68) encodes M11, a viral Bcl-2 homolog that can inhibit apoptosis induced by Fas and TNF-α in murine and human cell lines (Wang et al., 1999). Although homology between M11 and Bcl-2 is limited, structural analysis revealed that M11 has a BH3 binding groove that can sequester Bax and Bak (Loh et al., 2005). Moreover, viruses harboring a mutation that caused

defective BH3 binding exhibited impaired persistent replication and reactivation from latency *in vivo* (Loh et al., 2005). Recently, a novel viral mitochondrial antiapoptotic protein (vMAP) encoded by the M8 gene was identified (Feng et al., 2007). The N-terminal region of vMAP interacts with Bcl-2, which increases Bcl-2 recruitment to mitochondria and suppresses Bax activation. vMAP is necessary for viral replication in normal cells but not in Bax/Bak-deficient cells, suggesting that the antiapoptotic effect may counteract host innate immune responses.

Human papillomavirus (HPV) E1^E4 protein is encoded by spliced mRNAs that fuse the two early genes, E1 and E4, and is the most abundantly expressed viral protein in HPV-infected epithelia. In mature human keratinocytes, E1^E4 binds and collapses the cytokeratin network (Doorbar et al., 1991). Thereafter, E1^E4 translocates to mitochondria via an N-terminal leucine-rich region and induces the detachment of mitochondria from microtubules. The detached mitochondria then aggregate adjacent to the nucleus, which is followed by dissipation of $\Delta\psi_m$ and apoptosis. Other proapoptotic proteins encoded by E6 and E7 are multifunctional, at times preventing p53-induced apoptosis (E6) (Scheffner et al., 1990). E6 and E7 reportedly sensitize cells to several apoptotic stimuli in a manner that may or may not depend on p53 (Brown et al., 1997; Iglesias et al., 1998; Liu et al., 2000; Vikhanskaya et al., 2002).

3.2.2. RNA viruses

HCV encodes NS4A and NS3, two proapoptotic proteins that form a mitochondrial complex with NS3/4A and inhibit host innate immune responses by cleaving MAVS. NS4A localizes to mitochondria and alters their intracellular distribution, which is followed by dissipation of $\Delta\psi_m$ and cytochrome *c* release (Nomura-Takigawa et al., 2006). NS3, a viral protease, has been shown to induce caspase-8-mediated apoptosis independent of its protease activity (Prikhod'ko et al., 2004). Recently, the HCV core protein has been identified as a third proapoptotic protein that induces caspase-independent apoptosis-like effects such as membrane blebbing and nucleus condensation (Berg et al., 2009). Moreover, HCV encodes antiapoptotic proteins. NS2 is an ER-associated transmembrane protein that acts as an inhibitor of cell death-inducing DFFA-like effector B (CIDE-B)-induced apoptosis (Erdtmann et al., 2003). NS5A is also detected on ER of HCV-infected cells. This protein activates NF-κB to prevent cell death induced by ER stress (Waris et al., 2002). In addition, structural protein E2 has been shown to inhibit TRAIL-induced apoptosis via an unknown mechanism (Lee et al., 2005).

VSV is a rhabdovirus that causes neuronal apoptosis and the development of neuronal disorders (Licata and Harty, 2003). Cells infected with VSV exhibit early activation of the mitochondrial apoptotic pathway without viral protein synthesis or other replication events (Gadaleta et al., 2005, 2002; Gaddy and Lyles, 2005). The viral proteins matrix protein M and phosphoprotein P, an essential subunit of the viral RNA-dependent RNA polymerase complex, are involved in the induction of apoptosis via multiple pathways. M protein transcriptionally modulates Bcl-2 family proteins (Gadaleta et al., 2005), whereas the mechanism of action for phosphoprotein P is unknown (Das and Pattnaik, 2004).

Influenza A virus encodes a PB1-F2 protein that is inserted in the mitochondrial inner membrane via a C-terminal transmembrane region (Gibbs et al., 2003). Putative interacting partners for PB1-F2 include VDAC1 and ANT3, and it has been suggested that the proapoptotic activity of PB1-F2 results from enhanced MMP through direct interactions with other mitochondrial membrane proteins (Chanturiya et al., 2004).

Avian encephalomyelitis virus (AEV) belongs to the family *Picornaviridae*. Transient expression of the AEV structural protein VP3 and the nonstructural protein 2C was shown to promote cell death. VP3 was detected on mitochondria, where it induced apoptosis via the caspase-3-like protease pathway (Liu et al., 2002). 2C also localizes to mitochondria and promotes cytochrome *c* efflux into the cytosol, which in turn activates upstream caspase-9 and downstream caspase-3, leading to apoptosis (Liu et al., 2004). Although 2C is highly conserved among picornaviruses, the roles of 2C during viral replication remain unclear.

Severe acute respiratory syndrome corona virus (SARS-CoV) protein 7A is not required for viral replication in cultured cells, but it contributes to virus-induced apoptosis by inhibiting Bcl-xL (Schaecher et al., 2007; Tan et al., 2007). NSP15 protein, encoded by the SARS-CoV, inhibits apoptosis induced by overexpressed MAVS in a dose-dependent manner, but NSP15 does not inhibit staurosporine-induced apoptosis (Lei et al., 2009).

3.2.3. Reverse-transcribing viruses

Human immunodeficiency virus type 1 (HIV-1) encodes six accessory proteins that are not found in other classes of retroviruses. Viral protein R (Vpr) is a strong inducer of apoptosis (Stewart et al., 1997; Yao et al., 1998). When added to intact cells or purified mitochondria, synthetic Vpr causes rapid dissipation of $\Delta\psi_m$ and release of intermembrane space proteins through direct interactions with ANT or VDAC, components of the mitochondria PTPC (Jacotot et al., 2000). In lymphoid cells, Vpr-mediated MMP is facilitated by Bax binding to ANT, whereas it is prevented by Bcl-2 overexpression and PTPC inhibitors (Jacotot et al., 2000). Vpr is dispensable for HIV replication in T cells but not in macrophages. Interestingly, an R77Q mutation in Vpr abrogates its proapoptotic activity (Lum et al., 2003), suggesting that Vpr may be a crucial virulence factor during HIV infection. HIV envelope glycoprotein complex triggers MMP through a complex signal transduction pathway (Castedo et al., 2001; Perfettini et al., 2004). Tat also triggers apoptosis in infected and solely expressed cells and may cause neurodegeneration (Kruman et al., 1998; Li et al., 1995). Expression of Tat causes loss of $\Delta\psi_m$, reactive oxygen species overproduction, and caspase activation (Macho et al., 1999). Tat alters microtubule dynamics, which promotes proteasomal degradation of microtubule-associated protein 2 and activates apoptosis via a mitochondrial pathway (Aprea et al., 2006; Chen et al., 2002; Egelé et al., 2008). As a proapoptotic relative of Bcl-2 and transducer of death signals initiated by perturbed microtubule dynamics, Bim facilitates Tat-induced apoptosis (Chen et al., 2002). Nef protein induces lysosomal membrane permeabilization, leading to the release of Bax activator into the cytosol (Laforge et al., 2007). HIV-1 protease processes caspase-8, which processes Bid to its activated form (tBid) (Nie et al., 2002).

Human T lymphotropic virus type 1 (HTLV-1) causes adult T-cell leukemia and has also been associated with degenerative neuromuscular disease. The pX region of the genome encodes several proteins that can deregulate functional and transcriptional cellular activities (Yoshida, 2001). One such protein, p13II is localized on the mitochondrial inner membrane, where it produces a membrane potential-dependent influx of potassium, resulting in mitochondrial swelling and fragmentation and altered mitochondrial calcium uptake and retention (D'Agostino et al., 2005; Zamzami et al., 2005) p13II sensitizes cells to apoptosis induced by the Fas ligand and ceramide and suppresses cell proliferation and tumor genesis in cells coexpressing *myc* and *ras* (Silic-Benussi et al., 2004).

X protein from hepatitis B virus (HBx) contributes to the formation of hepatocellular carcinomas by acting as a transcriptional activator of viral or cellular genes (Kim et al., 1991). Associated with mitochondria, likely via a putative transmembrane region (aa 54–70) (Huh and Siddiqui, 2002), HBx sensitizes infected and transfected cells to TNF-α-induced apoptosis (Su and Schneider, 1997). HBx has also been shown to accumulate in the mitochondria of transfected hepatoma cells and interact with VDAC3, leading to $\Delta\psi_m$ dissipation and perinuclear aggregation of mitochondria (Henkler et al., 2001; Takada et al., 1999). Recently, it was shown that HBx induces the cyclophilin D-mediated mitochondrial permeability transition and causes calcium

influx into the cytoplasm (Tan et al., 2009). HBx also binds the mitochondrial matrix chaperone Hsp60 and interacts with Hsp70 (Tanaka et al., 2004; Zhang et al., 2005). Further studies are required to elucidate the mechanisms underlying HBx-related mitochondrial regulation.

4. HSV and mitochondria

HSV-1 and HSV-2 are large enveloped DNA viruses that possess at least 74 distinct genes. Approximately half of them are not essential for viral replication in cell culture, although they may be required during the viral life cycle in humans (Nishiyama, 2004). Herpesviruses, including HSV-1 and HSV-2, have developed a variety of strategies that allow efficient reproduction or promote latency. We are interested in the molecular basis of HSV pathogenesis, and here we summarize the results of recent studies on the roles of mitochondria during HSV replication.

4.1. HSV affects intracellular compartmentalization of mitochondria

We have shown that mitochondria respond to HSV infection by migrating with viral tegument proteins along microtubules to a site around the nucleus in which virion maturation and/or tegument assembly occur. Interestingly, levels of cellular ATP and lactate as well as $\Delta\psi_m$ are maintained for at least 6 h after infection before decreasing at later stages (Murata et al., 2000a). Earlier studies demonstrated that mitochondrial protein synthesis in HSV-infected cells decreases progressively, dropping to about 60% of normal levels (Latchman, 1988; Lund and Ziola, 1986). Moreover, mitochondria exhibit a gradual decline in the rate of calcium uptake, which reaches 65% of the control rate at later stages of infection (Lund and Ziola, 1985). These observations indicate that mitochondrial activity is negatively regulated by HSV infection. It is known that the viral assembly site of ASFV is cytoplasmic and surrounded by various organelles, including mitochondria (Rojo et al., 1998). Cristae condensation is observed at this position, indicating that the mitochondria are actively respiring. Accordingly, ASFV envelopment and capsid formation depend on calcium gradients and ATP (Cobbold et al., 2000). Thus, mitochondria surrounding the viral assembly site likely supply energy for viral morphogenesis. In HSV-infected cells, however, there is no evidence of enhanced mitochondrial activity, and the actual effects of mitochondrial clustering are not entirely clear.

The juxtanuclear accumulation of teguments, nucleocapsids, and mitochondria in HSV-2-infected cells shares some characteristics with aggresomes. We observed that disruption of these aggresome-like structures using nocodazole caused a small but consistent inhibitory effect (10-fold decrease) on the production of infectious particles (Nozawa et al., 2004) and proposed that the aggresome-like structures do not play a critical but an augumentary role in HSV-2 replication. Large clusters of mitochondria have also been observed near intracellular viral particle groups in HSV-1-infected human precursor oligodendroglial KG-1C cells without evidence of apoptosis (Bello-Morales et al., 2005). Therefore, during the early and late stages of infection, HSV may produce opposing effects on the localization and activity of mitochondria.

4.2. HSV UL7 localizes to mitochondria

HSV UL7 protein is expressed in the late phase of infection and is associated with intracellular capsids and virions in HSV-infected cells (Nozawa et al., 2002). The UL7 gene is not essential for HSV replication in cell culture, although mutant virus lacking UL7 formed small plaques compared to wild-type virus (Tanaka et al., 2008). UL7 is present in both mitochondria and cytoplasm and interacts with ANT2 and ANT4 in HSV-1-infected cells (Tanaka et al., 2008). ANT proteins (ANT1 to ANT4) are located in the mitochondrial inner membrane, where they are incorporated into PTPC and VDAC (Zhivotovsky et al., 2009). Further analysis is required to elucidate the functions of UL7, including any potential role as a regulator of apoptosis.

4.3. HSV UL12.5 degrades mitochondrial DNA

The HSV-1UL12 gene encodes two distinct proteins: UL12 and UL12.5. The former is an alkaline nuclease, and the latter is an N-terminally truncated 500-aa polypeptide that lacks the first 126 residues of UL12 (Bronstein et al., 1997). UL12 is known to play an important role in viral DNA replication and processing (Goldstein and Weller, 1998; Martinez et al., 1996). UL12.5 has also nuclease and strand-exchange activities but, unlike UL12, does not accumulate in the nucleus (Reuven et al., 2004). UL12.5 localizes predominantly to mitochondria, where it triggers massive degradation of mitochondrial DNA early during HSV replication (Saffran et al., 2007). Moreover, it has been suggested that UL12.5 acts directly within the mitochondrial matrix to degrade mitochondrial DNA through its nuclease activities (Corcoran et al., 2009). However, the biological significance of mitochondrial DNA depletion during the infection remains unclear.

4.4. US3 inhibits apoptosis

The genomes of HSV-1 and HSV-2 encode a viral serine/threonine protein kinase, US3, which is conserved in α-herpesviruses. US3 is not essential for viral replication in cell culture but is important for various aspects of HSV replication and pathogenesis (Kato et al., 2008; Kurachi et al., 1993; Reynolds et al., 2002). US3 expression markedly affects a number of signal transduction pathways including JNK (Murata et al., 2000b) and PKB/Akt pathways (Benetti and Roizman, 2006), and it is responsible for inhibition of mitochondrial electron transport in HSV-1-infected cells (Derakhshan et al., 2006). US3 protein kinase phosphorylates a large number of cellular and viral proteins in infected cells (Mou et al., 2007; Nishiyama, 2004; Roizman et al., 2007). Most importantly, US3 has a potent antiapoptotic activity in transfected and infected cells (Hata et al., 1999; Murata et al., 2002). For example, US3 is sufficient to block apoptosis induced by overexpression of Bad, Bid, and Bax (Munger and Roizman, 2001; Ogg et al., 2004). These results suggest that US3 exerts antiapoptotic effects via direct and/or indirect interactions with Bcl-2 family proteins. However, the precise mechanism underlying the antiapoptotic effects of US3 is still unknown (Benetti and Roizman, 2004; Mori et al., 2003; Poon et al., 2006). Recently, we demonstrated that a US3-inactivated HSV mutant showed selective and potent oncolytic activity against pancreatic tumor cells, suggesting that deletion of US3 is a promising approach for the development of oncolytic HSV (Kasuya et al., 2007).

5. Conclusions

We have summarized current knowledge of mitochondria-related signaling in virus-infected cells. Innate immune signals initiated at RLRs converge on mitochondria-associated adaptor molecules, which may prevent excessive immune responses that could be harmful to host organisms. In addition, recent studies have proposed another role for MAVS, that is, a proapoptotic activity for a non-CARD of MAVS in virus-infected cells (Lei et al., 2009; Yu et al., 2010). Further analyses are necessary to understand how the various roles of MAVS are regulated during early antiviral responses and the relationship between RLR ligand binding and MAVS-induced cell death. In this review, we have also described the profiles of mitochondria in HSV-infected cells, although the biological significance of these results is not entirely clear. Studies of the roles of mitochondria during viral infections will likely provide significant insights into immune

responses and broaden our understanding of this multifunctional organelle.

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